Access to Medications for Cardiovascular Diseases in Low- and Middle-Income Countries

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Abstract—Cardiovascular diseases (CVD) represent the highest burden of disease globally. Medicines are a critical intervention used to prevent and treat CVD. This review describes access to medication for CVD from a health system perspective and strategies that have been used to promote access, including providing medicines at lower cost, improving medication supply, ensuring medicine quality, promoting appropriate use, and managing intellectual property issues. Using key evidence in published and gray literature and systematic reviews, we summarize advances in access to cardiovascular medicines using the 5 health system dimensions of access: availability, affordability, accessibility, acceptability, and quality of medicines. There are multiple barriers to access of CVD medicines, particularly in low- and middle-income countries. Low availability of CVD medicines has been reported in public and private healthcare facilities. When patients lack insurance and pay out of pocket to purchase medicines, medicines can be unaffordable. Accessibility and acceptability are low for medicines used in secondary prevention; increasing use is positively related to country income. Fixed-dose combinations have shown a positive effect on adherence and intermediate outcome measures such as blood pressure and cholesterol. We have a new opportunity to improve access to CVD medicines by using strategies such as efficient procurement of low-cost, quality-assured generic medicines, development of fixed-dose combination medicines, and promotion of adherence through insurance schemes that waive copayment for long-term medications. Monitoring progress at all levels, institutional, regional, national, and international, is vital to identifying gaps in access and implementing adequate policies. (***Circulation*. 2016;133:2076-2085. DOI: 10.1161/CIRCULATIONAHA.115.008722.)**

Key Words: cardiovascular diseases ■ delivery of health care ■ drug therapy ■ essential drugs ■ health services accessibility ■ medication adherence ■ policy

Medicines are an essential building block of a functioning health system and represent a substantial part of total health expenditure.[1] The objectives of this review are to give an overview of access to medication for cardiovascular disease (CVD) from a health system perspective[2] and to describe strategies that have been used to promote access, including providing medicines at lower cost, improving medication supply, ensuring medicine quality, promoting appropriate use, and managing intellectual property issues.

A comprehensive systematic review is outside the scope of this article. Instead, we summarize key evidence in published and gray literature related to advances in access to cardiovascular medicines using the 5 health system dimensions of access: availability, affordability, accessibility, and acceptability (Table 1).

Burden of CVD and Risk Factors

CVDs represent the leading causes of death globally,[3] with an estimated 17.3 million deaths in 2013, representing about a quarter of all global mortality.[4] Approximately 80% of these deaths occur in low- and middle-income countries (LMICs).[5] Ischemic heart disease and stroke are the number 1 and 3 causes of death, respectively, according to the Global Burden of Disease estimates of 2013.[4] The rise in global CVD prevalence is rooted in part in demographic shifts (population growth and aging) and the increased prevalence of risk factors (elevated blood pressure, diabetes mellitus, smoking, alcohol, obesity, lack of exercise, and unhealthy diet).[6]

LMICs bear the principal burden of other CVDs, particularly rheumatic heart disease and heart failure. Rheumatic heart disease is more prevalent in LMICs than in high-income countries and may affect up to 36 million people worldwide.[7,8] Primary and secondary prevention programs rely on long-term penicillin therapy. Multiple registries in rural and urban low-income countries document the predominance of heart failure as the principal manifestation of CVD.[9–11]

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Guest Series Editor is Scott D. Solomon, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.008722/-/DC1.

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***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.115.008722**

Table 1. Five Health System Dimensions of Access to Medicines

Dimension	Description	Measures (Examples)
Availability	Relationship between type/quality of medicine required and type/quality of medicine delivered	Ratio of type of medicines in stock at the time of the inspection and type of medicines that should be available (often expressed as percent)
Affordability	Ability of the user to pay for the product	Ratio of price and income Percentage of household income or assets spent on medicines.
Accessibility	Ability of an individual to access care when needed	Travel time to nearest facility Proportion of patients not being able to access a facility when needed in the last month
Acceptability (adoption)	The use of medicines, including appropriate prescription by providers and adherence by patients	Proportions of prescriptions according to local guidelines Proportion of patients adherent to treatment over the last year
Quality of medicines	Medicines produced by manufacturers and authorized by the national medicines regulatory authority that meet quality specifications set by national standards (correct dose of active ingredient, dissolution time)	Proportion of medicines failing the quality test Total number of medicines tested

Pharmacotherapy as Prevention and Treatment

In addition to lifestyle interventions to mediate modifiable risk factors, medications are integral to CVD control strategies. Blood pressure–lowering therapy using 1 or a combination of medications is key in the prevention and treatment of CVD. Globally, ≈62% of cerebrovascular and 49% of ischemic heart disease have been attributed to suboptimal control of blood pressure.[12] Because abnormal blood lipids have been established as a major CVD risk factor, the development of medicines to lower lipids has had an important impact on the prevention and treatment of CVDs. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) can reduce the risk of major cardiovascular events by 20%, and the benefits of statin therapy increase with duration.[13,14] In addition, antiplatelet drugs such as low-dose aspirin have an important role in preventing ischemic heart disease and stroke.[15] Because the mechanisms of action of major pharmacotherapeutic options for CVD (blood pressure–lowering, lipid-lowering, and antiplatelet drugs) are largely independent, fixed-dose combinations (FDCs) of these effective medicines have been promoted.[15]

Among the "best buy" prevention and control interventions for CVD identified by the World Health Organization (WHO) is multidrug therapy for patients with ≥30% risk of developing heart attack and stroke within 10 years.[16] Such therapy includes blood pressure–lowering medicines, blood glucose control for patients with diabetes mellitus, lipid-lowering medicines, and antiplatelet medicines for secondary prevention of myocardial infarction.[17,18]

In LMICs, medication therapy for secondary prevention of rheumatic fever with intramuscular penicillin is cost-effective.[19] Heart failure caused by cardiomyopathies, hypertension, and rheumatic heart disease requires long-term therapy with combinations of diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers.[20] Ideal medical therapy for the array of CVD in LIMICs will require access to several classes of CVD medicines addressing both endemic and emerging CVDs.

However, despite the clear evidence base for medicines to prevent and treat CVD, there is a wide gap between patients in need of treatment and those who actually receive it. Several large-scale studies have been conducted to estimate the access gap to CVD treatment. A literature review by Ibrahim and Damasceno[21] estimates the percentage of patients diagnosed with hypertension but not adequately controlled; the authors found that only 10% of all patients with identified hypertension had blood pressure within the target range.

Two large, multicountry studies, the WHO Prevention of Recurrences of Myocardial Infarction and Stroke (PREMISE)[22] study and the Prospective Urban Rural Epidemiological (PURE) study,[23] assessed the use of secondary prevention therapy for CVD predominantly in urban and rural areas of LMICs. The PREMISE study analyzed whether patients received the indicated therapy.[22] The authors found that in 10 LMICs the proportion of patients with CVD who had received medications was low for β-blockers (48% for coronary heart disease), ACE inhibitors (40% for coronary heart disease and 38% for stroke), and statins (30% for coronary heart disease and 14% for stroke). The PURE study analyzed the use of 5 therapeutic classes in 17 LMICs among patients with known CVD. Only a quarter of CVD patients (25%) reported receiving antiplatelet drugs, 17% received β-blockers, 20% received ACE inhibitors or angiotensin receptor blockers, and 15% received statins.[23] A country's economic level had a greater effect on the probability of taking medicines than individual factors such as age and sex.[23]

Whereas the previously mentioned studies examined access across different countries, a more recent large, multinational study evaluated within-country variation in access to cardiovascular medicines.[24] Analysis of household data from 6 countries (Cambodia, Colombia, Iran, Malawi, South Korea, and the United States) showed that about two thirds of individuals in high-income countries were receiving treatment for hypertension compared with <50% of individuals in low- or lower-middle-income countries.[24] Within-country differences were large in Colombia, Iran, Malawi, and South Korea.

Improving access to medicines for CVD is an essential component of worldwide programs to reduce the access gap to treatment for CVD.

The 5 Dimensions of Access to Medicines

There is not 1 universally accepted definition of access to medicine. A widely used construct describes 5 dimensions of access: availability, affordability, accessibility, acceptability, and quality of medicines as a cross-cutting dimension (Table 1).[25] Availability refers to the relationship between the type and quantity of a medicine required and type and quantity delivered. Affordability refers to the ability of the user to pay for the product measured as the ratio of medicine price and household income.[26] Factors affecting affordability are patent status of the medicine, market authorization requirements, and pricing and reimbursement policies, among others. Accessibility refers to the ability of the person to access medicines when in need; it considers travel distance and time, as well as opening hours of facilities, ability to be seen, etc. Acceptability, also referred to as adoption, describes how medicines are used in real-world settings, including their appropriate prescription by providers according to evidence-based guidelines and adherence by patients.[27] Finally, quality of medicines refers to the standards defined and approved by the national medicines regulatory authority such as dose of active ingredient and dissolution time for tablets. A substandard medicine is one that is produced by manufacturers and authorized by the national medicine regulatory authority but does not meet quality specifications set by national standards (inadequate dose of active ingredient, longer dissolution time, etc).[28] What medicines should be given priority in decisions about financing and provision? The biannually updated WHO Model List of Essential Medicines serves as a guide for countries to draft their own prioritized medication list to address the local health needs.[29] Medicines are selected via an evidence-based process, with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness, but the comparative cost-effectiveness has been shown to be difficult to apply at global level.[30] The current 19th model list includes 23 different CVD medicines (Table 2).[31] More than 123 countries have an essential medicine list. However, a study from 13 countries in sub-Saharan Africa found that 40% of countries had not updated their essential medicine list in the last 5 years.[32] Large differences exist among medicines included in the national essential medicine list that cannot be explained by variation in disease burden or clinical guidelines alone (Figure). We evaluated the available country essential medicine lists for the presence of key medicines necessary for secondary prevention of CVD, including low-dose aspirin (≤150 mg), β-blocker, ACE inhibitor, and statin. Countries are grouped by The World Bank income classification (http://data.worldbank.org/about/country-and-lending-groups). A full list of the countries included is available in Table I in the online-only Data Supplement. High-income countries are excluded because only 13 have available essential medicine lists. β-Blockers and ACE inhibitors are the therapeutic groups listed by most countries (≈90%); aspirin and statins are listed less frequently. Low-income countries in general include CVD medicines less frequently than higher-income countries. The lower percentage of statin inclusion in the national essential medicine list in low-income countries may be related to the lower prevalence of hyperlipidemia compared with high-income settings.[33] However, heart

Table 2. List of CVD Medicines Included in the WHO Model List of Essential Medicines[31]

Therapeutic Group According to EML	International Nonproprietary Name
Antithrombotic agents	Streptokinase
Cardiac glycosides	Digoxin
Antiarrhythmics, class I and III	Lidocaine
	Amiodarone
Cardiac stimulants excluding cardiac glycosides	Dopamine
	Epinephrine
Vasodilators used in cardiac diseases	Glyceryl trinitrate
	Isosorbide dinitrate
Antiadrenergic agents, centrally acting	Methyldopa*
Arteriolar smooth muscle agents	Hydralazine
Low-ceiling diuretics	Hydrochlorothiazide
High-ceiling diuretics	Furosemide
	Mannitol
Potassium-sparing agents	Spironolactone
	Amiloride
β-Blocking agents	Bisoprolol
	Carvedilol
	Metoprolol
Selective calcium channel blockers with vascular effects	Amlodipine
Selective calcium channel blockers with direct cardiac effects	Verapamil
ACE inhibitors, plain	Enalapril
Lipid-modifying agents	Simvastatin
Other analgesics and antipyretics	Acetylsalicylic acid
Medicines affecting coagulation	Heparin sodium
	Warfarin
B-Lactam antibacterials†	Benzathine benzylpenicillin
	Phenoxymethylpenicillin
Insulins and other medicines used for diabetes mellitus‡	Glicazide
	Glucagon
	Insulin injection
	Intermediate-acting insulin
	Metformin

ACE indicates angiotensin-converting enzyme; CVD, cardiovascular disease; EML, essential medicine list; and WHO, World Health Organization.

*"Methyldopa is listed for use in the management of pregnancy-induced hypertension only. Its use in the treatment of essential hypertension is not recommended in view of the availability of more evidence of efficacy and safety of other medicines."[31]

†For the prevention of rheumatic heart disease.

‡We listed these medicines because they are included in the "best buy" strategies of the World Health Organization to reduce cardiovascular diseases. This article focuses on access to medicines for cardiovascular disease, not specifically to these medicines.

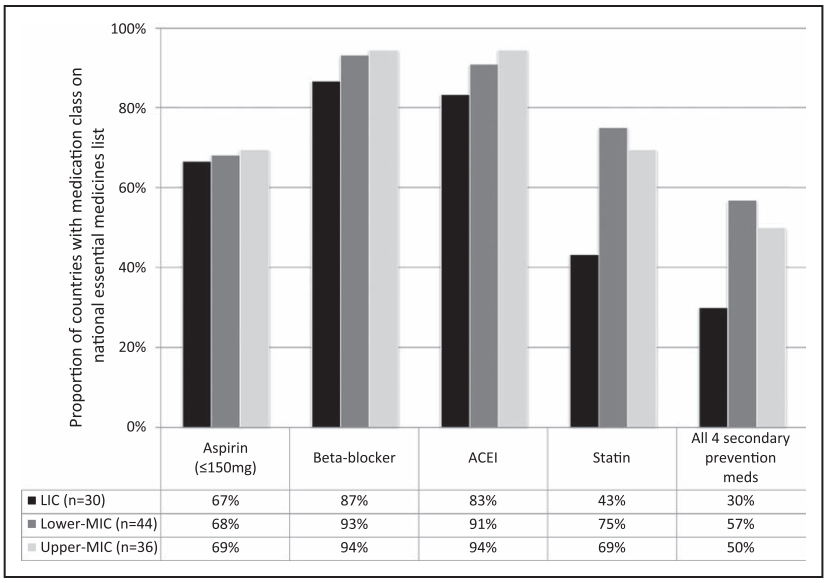

Figure. Proportion of countries with secondary prevention medication class on the national essential medicine list by income status (n=110). High-income countries were excluded. ACEI indicates angiotensin-converting enzyme inhibitor; LIC, low-income country; and MIC, middle-income country.

failure–specific β-blockers are less frequently listed in low-income countries (17%) compared with lower-middle- (55%) and upper-middle- (47%) income countries, even though heart failure among CVD patients is common in low-income settings.[9–11] Taking all 4 secondary prevention therapeutic groups together, only about half of the countries include at least 1 medicine of each group on their essential medicine list.

Availability of Cardiovascular Medicines

To measure availability of medicines, Health Action International (HAI) and the WHO have conducted standardized surveys in >70 countries. The HAI/WHO methodology assesses availability during facility inspections, noting whether a medicine that should be in stock is or is not physically present.[34] A meta-analysis of surveys from 36 countries assessed access to 5 cardiovascular medicines of different classes: atenolol, captopril, hydrochlorothiazide, losartan, and nifedipine.[35] The authors found that cardiovascular medicines were available in only 26% of public and 57% of private facilities.[35] In general, availability of generic medicines for acute conditions was higher than for chronic conditions in both public and private sectors. For the public sector, availability was 54% for a basket of generic medicines for acute conditions and 36% for generic medicines for chronic conditions (P=0.001). For the private sector, availability was 66% for generics for acute conditions and 54% for generics for chronic conditions.[36]

Affordability of Cardiovascular Medicines

Affordable medicines should be purchased at prices that do not distress a household's finances. Medicine prices can be compared with the international reference price: the median of the actual procurement prices for medicines offered to low- and middle-income countries by nonprofit drug suppliers and international tender prices. It has been used widely to compare local prices with a benchmark price internationally using the HAI/WHO methodology. The HAI/WHO methodology defines affordability relative to the salary of the lowest paid government worker. Other methods define medicine as unaffordable when the total cost exceeds 20% of the household capacity to pay.[34]

The HAI/WHO standardized survey results in >70 countries also provided relevant information on affordability of cardiovascular medicines. Although the prices of government-procured generic medicines varied from 1.5 to 3 times the international reference prices, the same generic products sold to patients cost ≈15 times the international reference prices in the public sector and ≈30 times the international reference prices in the private sector.[37] Treatment for CVD in general was not affordable in the majority of countries, particularly in low-income countries.[35] In the public sector, a 1-month supply of 1 generic CVD medicine cost on average 2.0 days' wages, and 1 originator brand CVD costs on average 8.3 days' wages for the lowest paid government worker. Atenolol was the most affordable of all cardiovascular medicines studied (1.1 days' wage). Combination therapy for CVD is largely unaffordable. Since the publication of the Cameron et al[37] article in 2009, 9 peer-review publications reporting 20 additional surveys have demonstrated similar findings.[34] Importantly, postmanufacture costs are generally borne by patients and include duties, taxes, markups, and additional charges. A recent study evaluated the affordability of combination therapy (aspirin, β-blocker, ACE inhibitor, and statin) for the secondary prevention of CVD using a threshold of 20% of a household's capacity to pay. In lower-middle- and low-income countries, a 4-drug combination was not affordable for 33% and 60% of households, respectively.[38]

The patent status of a medicine affects access because of the effects on affordability. Medicines that are protected by patents are on average more expensive and less affordable than off-patent medicines because patented medicines generally lack market competition. According to information from the US Food and Drug Administration[39] and the European Patent Office,[40] there appear to be no unexpired patents on 5 commonly used cardiovascular medicines: atenolol, captopril, hydrochlorothiazide, losartan, and nifedipine. Patents should not represent a major access barrier to CVD monotherapy in

the United States and Europe. Additionally, several patented combinations of medicines in the same classes in the US market (atenolol/chlorthalidone and losartan/hydrochlorothiazide) have already expired. However, there are 12 existing US patents on adult and pediatric hydrochlorothiazide combinations that will expire in the next decade. The existence of patents on these combinations that include hydrochlorothiazide may also present a barrier to their affordability in other countries where such patent protection may also exist for these particular combinations (Tables II and III in the online-only Data Supplement).

Apart from price and its relation to patents, affordability is closely related to financing. There is substantial evidence that an increase in copayments for medicines results in a decrease in use of the medicine; however, the only evidence available comes from high-income countries.[41] Most high-income countries have instituted some form of social protection in which individuals are insured against large health care–related expenditures, including the cost of medicines.

Health financing in LMICs is particularly relevant for chronic CVD medicines, for which expenditures are recurrent. One example of an insurance program that includes medicines for a number of CVD in the outpatient benefit package is Seguro Popular in Mexico. A 2005 household survey showed that beneficiaries had a 50% higher probability of receiving antihypertensive treatment and achieving blood pressure control than nonbeneficiaries.[42] Selection bias may exist because enrollment in Seguro Popular is voluntary. However, because affiliation in Seguro Popular is high among previously uninsured people, it is difficult to argue that the effect of this insurance program on use of CVD medicines is due purely to motivation.

Accessibility of CVD Medicines

Accessibility is another important dimension of access to medicines. Medicines may be available at affordable prices in a given region of a country. However, patients must be able to obtain the medicines.[43] In some low-income countries, absenteeism of public-sector health workers may be as high as 35% to 68%.[44,45] Poor accessibility is related to suboptimal management of hypertension and secondary prevention of CAD. In Ethiopia, living within 30 minutes of a public-sector hospital was associated with improved adherence to antihypertensive therapy.[46]

A recent household study from 5 low- and middle-income countries (Uganda, Philippines, Kenya, Ghana, and Jordan) shed light on how geographical location may influence accessibility to medicines for noncommunicable disease (NCD), although the findings are not consistent.[47] Ugandan household members living in the capital had increased access to NCD medicines. One underlying reason may be long travel time to the health facility: In Uganda, 35% of households had to travel >15 minutes to reach a health facility. In contrast, in Jordan, only 5% of households had no health facility within 15 minutes' travel time. With just 16% of Ugandan households having access to medicines for NCDs, it was the country with the lowest percentage. Jordan had the highest percentage (49%).

Acceptability of Cardiovascular Medicines

Medicines for CVD must be acceptable to both providers and patients, and a host of factors affect behavior for both groups. Patients hospitalized for acute coronary syndromes in India experience wide variation in care. Notably, patients in the lowest socioeconomic classes are less likely to receive evidence-based treatment, including aspirin, β-blockers, statins, and thrombolytics, even when treated in the same hospital as people of higher socioeconomic classes.[48]

One study of patients with heart failure in a rural hospital in Haiti where medicines were both available and free for patients illustrates the barrier to provider acceptability. On discharge, only 21% of patients with heart failure caused by cardiomyopathy were treated with the evidence-based combination of diuretic, β-blocker, and ACE inhibitor.[10] Changing provider behavior will require multifaceted approaches. A systematic review of barriers of hypertension management noted that providers frequently disagreed with clinical recommendations.[49]

Secondary prevention of rheumatic heart disease requires long-term penicillin, and injections are more efficacious than oral administration.[50] However, because of the perceived high risk of anaphylaxis with penicillin and reuse of needles, there is still resistance to using intramuscular penicillin among some providers. The perceived safety issues have even resulted in government regulations prohibiting penicillin injections in hospitals and clinics in parts of India in the past.[51] Locally adapted clinical guidelines inclusive of local government and civil society organizations will be needed to improve physician acceptability in using cardiovascular medicines.

Among patients, forgetting to take 1 or several medicines is a key barrier to adherence.[52] Because CVD risk reduction requires modifying several risk factors, polypharmacy is often the norm. To address acceptability of prevention and treatment, various authors[53–55] have suggested that a combination of several cardiovascular medicines in 1 FDC form ("polypill") would increase adherence, reduce delivery costs, and ease supply-chain burdens. FDCs have been used successfully to treat other conditions, including HIV, tuberculosis, and hypertension. Polypills with different components have been proposed for either primary or secondary prevention of CVD.[52] A 2004 WHO report identified the polypill as having potential value for secondary prevention in patients with existing CVD and recommended a research agenda.[53,54] In 2009, The Indian Polycap Study (TIPS) demonstrated that a 5-drug polypill was well tolerated.[55] The Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) trial showed a positive effect on adherence and intermediate outcome measures such as blood pressure and low-density lipoprotein cholesterol levels.[56]

Adequately powered, large-scale, clinical trials will be needed to detect differences in clinically important outcomes such as mortality, to assess the safety of combinations, and to evaluate unintended collateral harms such as neglecting improved diet and exercise as a result of the perceived security of improved medication adherence.[57] Such studies would need to be publicly funded because the components in the different polypills are all individually off patent and the cost of

Table 3. Selected Strategies to Promote the Quality of Medicines

Strategy	Description
Strengthen the capacity of the NMRA	Through promoting changes in organizational processes and human resource training, increasing the capability of the NMRA to inspect manufacturers and to promote quality of medicines
Promote the prequalification program	Program supported by the WHO whereby international experts collaborate with NMRAs in evaluation and inspection activities Building national capacity for sustainable manufacturing and monitoring of quality medicines
Create a business environment that is favorable for the private sector to invest in secure supply chains	For instance, through providing incentives (eg, low-interest loans or tax breaks) so that businesses are more inclined to invest in manufacturing of quality medicines
Regular quality testing at procurement and sales sites	Judging the quality of medicines is very difficult without specific equipment and expertise; having organizational policies in place to procure only from certified suppliers and to conduct regular quality testing reduces the risk of substandard medicines
Consumer SMS and mobile application verification of product authenticity	During purchase, consumers can check whether the product is authentic by sending an SMS with a unique product label number

NMRA indicates National Medicines Regulatory Authorities; SMS, short message service; and WHO, World Health Organization. Adapted from *Countering the Problem of Falsified and Substandard Drugs*.[60] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

undertaking such large trials is likely beyond the means of generic manufacturers.[15,58]

Quality of Cardiovascular Medicines

In addition to the other 4 access dimensions, the risk of substandard quality or falsification of medicines must be managed to achieve desired health outcomes. The concern about the low quality of medicines is shared among all countries regardless of income category.[60,61] Substandard medicines can be defined as those produced by manufacturers and authorized by the national medicine regulatory authority that do not meet quality specifications set by national standards (lower dose of active ingredient, longer dissolution time, etc).[60] However, markets with less control over imports, distribution chains, and retail outlets are more vulnerable to low-quality product entry.[62] Falsified medicines can be defined as those that "carry a false representation of identity, or source, or both," and many falsified medicines are also substandard.[62] Quantifying the problem of substandard or falsified medicines is difficult because quantification is resource intensive and fraught with methodological challenges such as a lack of information on market size. A study in Rwanda focusing on cardiovascular medicines that showed 2 of 10 products purchased from private outlets were substandard.[61] There are, however, multiple strategies to address substandard quality of medicines (Table 3). A discussion of each individual strategy is beyond the objectives of this article. Instead, we provide 2 examples: one focusing on medicines procurement and the other on the consumer. An intervention at the level of procurement is the regular quality testing carried out by large procurement agencies aimed at selecting only manufacturers or distributors that consistently supply products that pass the quality tests. A consumer-side intervention is the printing of a unique code on the product for verification. At the point of purchase, consumers can scratch off a label revealing the code that can be sent via short message service to a central database.[62] The consumer will receive an instant response verifying or refuting the authenticity of the product. Medicine manufacturers selling their products on the Nigerian pharmaceutical market have used such a verification system.[63]

Discussion and Recommendations

Challenges

Many challenges to improving access to CVD medicines remain (Table 4). First, inequity in access to medicines is a serious barrier to achieving universal health coverage. The adoption of financial protections in the form of tax-based or obligatory insurance is one important step, although it will take many years for countries currently investing in coverage scale-up to effectively provide for all their population.[65] Monitoring progress not only in terms of availability and affordability of medicines in health facilities but also in terms of equity of access is relevant. The WHO is building a consensus on indicators to measure equity in access to care, including medicines, in relation to universal health coverage.[66] Even though the proportion of household income spent on medicines would be a suitable measure, it is difficult to implement because of a lack of resources to collect periodic data. However, it is expected that with the need to measure progress on universal healthcare coverage, more countries will move toward collecting health care–related expenditure, including medicines, from household surveys.

With respect to patent protection, we note that the US Food and Drug Administration has recently finalized a new policy that will for the first time allow new FDC drugs consisting of at least 1 new drug product to be eligible for 5 years of "new chemical entity" market exclusivity, even if the other components of the combination have already been marketed and regardless of any patent. For companies with existing FDCs on the US market, the US Food and Drug Administration will not apply the policy retroactively.[67] The patenting of FDCs for CVD will pose a challenge to generic manufacturers

Table 4. Challenges and Future Directions

Challenge	Suggested Next Step
Availability	
Low availability of essential medicines for CVD in public and private facilities	Improve the selection process of essential medicines Increase financing for essential medicines for CVD Create incentives in the public and private sectors to make low-price, quality-assured medicines available
Affordability	
Markups along the medication distribution chain	Abolish taxes and duties on essential medicines and control markups
Unaffordable prices	Pooled procurements in specific contexts may work (eg, harmonization of product regulations)
Patents/marketing combinations of nonpatent medications	Require proof of improved clinical efficacy for a "new" form of previously known combination (see section 3(d) of Indian Patent Law[64]) Incentivize innovation by allowing market exclusivity for fixed-dose combination as long as 1 component is a new chemical entity
Lack of financing for medications	Scale up insurance programs to include a basic package of financial protection (universal health coverage, social protection)
Drug manufacturer profitability	Provide incentives to businesses to invest in quality medicines
Accessibility	
Short hours of clinic operation	Increase operational hours of clinics providing free or subsidized care
Long waiting times	Decrease waiting times by streamlining organizational processes and changes in regulations
Low perceived quality of care	Increase perceived quality of care, eg, patient satisfaction surveys to monitor changes and identify gaps and needs.
Acceptability	
Multiple medications needed for CVD prevention	Provide FDC medications (polypill) Perform large population-based studies to demonstrate efficacy, safety, and acceptability of FDCs
Quality of medicines	
Substandard quality of essential medicines for CVD	Provide incentives to businesses to invest in quality medicines Follow good procurement practices Trace and track at the point of product purchase to verify authenticity of the product

CVD indicates cardiovascular disease; and FDC, fixed-dose combination.

wishing to enter the market, especially in jurisdictions that continue, at least in the foreseeable future, to have reduced requirements for substantive patent examination (eg, South Africa, Malaysia, France, Italy, Spain, Switzerland, Belgium, and Israel).[68] The Indian Patent Act[64] offers a useful model: Unless a new form of an already-existing CVD FDC shows increased efficacy, it should not be patentable. If it demonstrates increased efficacy, then it is treated as an altogether new and potentially patentable substance.

Currently, donor support to finance prevention and control of NCDs, including CVD, is sparse compared with other areas such as HIV. Unprecedented, continuous donor support for more than a decade made it possible to achieve increased access to antiretroviral therapy globally. However, only 0.6% of all development aid for health was spent on NCDs in 2010.[69] Access to medicines for NCDs is lagging. The costs of providing the best buy strategies recommended by the WHO, a multidrug regimen for individuals at high risk of CVD plus measures to prevent cervical cancer, have been estimated at US $1 per person per year in low-income countries, less than US $1.5 in lower-middle income, and US $2.5 in upper-middle income countries.[70] Even though these might be affordable to middle-income countries, low-income countries might still depend on donor support.

Opportunities

From a health system perspective, there are many important opportunities to accelerate progress to medicines access for CVD. First, 192 countries expressed their commitment to lower NCD mortality 25% by 2025. One of the key strategies to achieve this goal is to increase availability to essential medicines for the prevention and treatment of CVD, in

particular those medicines that are key for secondary prevention of myocardial infraction and stroke (antiplatelet drugs, β-blockers, ACE inhibitors, statins). The indicator to measure this voluntary country goal is the availability of essential CVD medicines at health facilities with a target level of 80%, which means that medicines in all 4 of the key categories are in stock at the time of the inspection in 80 of 100 facilities.[71] In addition, regular monitoring with a standardized method needs to be addressed.[72]

Second, with respect to affordability, production costs of the large majority of cardiovascular medicines are low, making them, in theory, affordable to countries of all income levels. Promotion of low-cost, quality-assured generic medicine policies is critical, not only in the public sector and within insurance schemes but also in the private sector. At the same time, it is important that production remains profitable to manufacturers. It has been reported that for some cardiovascular medicines such as thiazide diuretics, production was abandoned in some countries because the price was too low to allow a sufficiently large profit margin to make production attractive to the manufacturer.[73]

Third, in terms of accessibility and acceptability, new delivery mechanisms such as the polypill for secondary prevention have the potential to increase availability and adherence and to result in a higher impact on health outcomes than traditional multidrug regimens. Some clinical trials have already shown promising results. Additionally, combination therapy might offer logical advantages: simplification in the procurement process and savings in the supply chain.

Improving access to medicines for CVD is a key strategy to substantially decrease morbidity and mortality from NCDs globally. The foundation has been laid by the commitment of 192 countries to achieve a reduction in NCD mortality of 25% by 2025. The health systems approach presented here can help to develop more comprehensive strategies to achieving universal access to cardiovascular medicines in the coming years in all countries.

Source of Funding

Dr Kwan was funded by the Research Career Development Program in Vascular Medicine (National Institutes of Health/National Health, Lung, and Blood Institute K12HL083781).

Disclosures

None.

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